Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a clinical practice guideline

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CRD summary
This review concluded that neither gefitinib nor erlotinib should be used in conjunction with first-line platinum-based chemotherapy or as maintenance therapy for advanced non-small-cell lung cancer (NSCLC). Erlotinib monotherapy can be recommended for second-line or later treatment of patients with recurrent or relapsed NSCLC. The conclusions follow the results of the review, however, incomplete reporting of the review methods undermines their strength.

Authors' objectives
To evaluate the role of the epidermal growth factor receptor (EGFR) inhibitors gefitinib and erlotinib for patients with advanced non-small-cell lung cancer (NSCLC).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched to 2005, and Cancerlit to 2002, for eligible studies; the search terms were provided. The following conference proceedings were also searched: the American Society of Clinical Oncology (to 2005), the International Association for the Study of Lung Cancer (to 2005), the European Society for Medical Oncology (to 2004) and the European Cancer Conference (to 2003). Data from slide presentations linked to abstracts were included if published on meeting websites. In addition, the CMA Infobase and the National Guideline Clearinghouse were searched for relevant evidence-based guidelines. The references from relevant articles and reviews were screened for additional studies. Non-English language studies were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) (phase II or phase III) were eligible for inclusion, either published in full or as abstracts.

Specific interventions included in the review
Studies that compared gefitinib or erlotinib (alone or in combination with chemotherapy) with placebo, best supportive care (BSC), chemotherapy, or different regimens of gefitinib or erlotinib were eligible for inclusion. In the review the EGFR inhibitors (250 to 500 mg gefitinib or 150 mg erlotinib) were given with standard first-line or subsequent chemotherapy, as maintenance therapy after chemoradiation and consolidation therapy, or alone. Controls included chemotherapy, placebo and BSC. Different doses of gefitinib were compared with each other.

Participants included in the review
Studies of patients with advanced NSCLC were eligible for inclusion. Studies in the review included patients with advanced, recurrent or relapsed NSCLC.

Outcomes assessed in the review
Studies reporting symptom control, quality of life (QOL), tumour response or survival rates were eligible for inclusion. The review also reported data on toxicity.

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies for inclusion. The authors did not describe whether they made decisions independently or how any disagreements were resolved.

Assessment of study quality
The authors referred to an assessment of validity but did not clearly state what criteria they used or how the assessment was performed.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many authors performed the data extraction.

Dichotomous data were extracted as percentages experiencing the event in each group. Continuous survival data were expressed as group medians. Differences between the groups were expressed as p-values and/or hazard ratios (HRs) with confidence intervals (CIs).

**Methods of synthesis**
How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
Individual differences between the studies were highlighted in the body of the text.

**Results of the review**
Twelve RCTs (n=7,724) were included. Seven were fully published (n=6,037) and 5 were in abstract form (n=1,687).

Of 9 RCTs evaluating gefitinib, 5 were fully published articles, all of which were double-blinded. Four of the 5 published articles conducted intention-to-treat analyses and/or followed up 99% of the participants. The phase III studies (4 of the 5 published articles) utilised data-monitoring committees. Limited data were available on the quality of the 4 RCTs of gefitinib reported as abstracts or slide presentations. Of the 3 RCTs of erlotinib (all phase III), 2 of which were fully published, at least 1 was double-blinded and analysed by intention-to-treat. Nine of the 12 studies reported associations with pharmaceutical companies.

**Gefitinib.**

First-line treatment (2 RCTs, n=2,130).

Among patients on platinum-based chemotherapy receiving concurrent gefitinib (250 or 500 mg) or placebo, there were no statistically significant differences at 12 months between the groups for symptom control, survival, tumour response or median time to progression. Adverse events were similar in all study arms, with the exception of dose-related diarrhoea and skin disorders associated with gefitinib. Withdrawal from treatment due to adverse events (2 RCTs) and infections (1 RCT) were also significantly more common in the gefitinib arms, especially the 500-mg arm. Maintenance therapy (1 RCT, n=255).

Among patients with unresected NSCLC without disease progression after chemoradiation and consolidation therapy, who were receiving gefitinib (250 mg) or placebo as maintenance therapy, there was no statistically significant difference in survival rates between the groups.

Second-line or later treatment (2 RCTs).

In one RCT (n=1,692) gefitinib provided no statistically significant overall survival benefit over BSC for patients who failed to respond or could not tolerate chemotherapy, though symptom scores were significantly more improved in the intervention group (p=0.019). Subgroup analysis showed a statistically significant benefit in survival times among patients who had never smoked (HR 0.67, 95% CI: 0.49, 0.92) and among patients of Asian origin (HR 0.66, 95% CI: 0.48, 0.91). A second RCT, comparing docetaxel with gefitinib (250 mg), reported similar tumour response, median survival rates and QOL outcomes in the two groups.

Dose comparisons (2 RCTs, n=425).
Among patients with relapsed or recurrent NSCLC, tumour response and survival rates were similar among patients on 250 or 500 mg gefitinib. The median time to symptom improvement in symptomatic patients was 8 days (1 RCT). Toxicity was generally higher in the 500-mg group.

The review also referred to preliminary data from 2 RCTs of gefitinib used as first- or second-line therapy in combination with chemotherapy.

Erlotinib.

First-line treatment (2 RCTs, n=2,231).

Among patients on platinum-based chemotherapy receiving concurrent and maintenance erlotinib (150 mg) or placebo, there were no statistically significant differences overall between the groups in survival, time to disease or symptom progression rates. In subgroup analysis, never-smokers in 1 RCT had significantly increased median survival time (22.5 months versus 10.1 months, p=0.001) and time to disease progression (6 months versus 4.3 months, p=0.002). Among patients receiving erlotinib those with EGFR mutations had a significantly higher tumour response rate than those without (53% versus 18%, p<0.01), though there was no statistically significant difference in survival rates. The difference in tumour response rate did not apply in the placebo group. One of the RCTs reported a higher incidence of serious adverse events in the erlotinib arm.

Second-line or later treatment (1 RCT, n=731).

Among patients with relapsed or recurrent NSCLC taking erlotinib or placebo, a statistically and clinically significant benefit was reported in median overall survival (6.7 months versus 4.7 months; HR 0.61, p<0.001) and progression-free survival (2.2 months versus 1.8 months; HR 0.61, p<0.001) in the erlotinib group. In this group, tumour response rates were higher among women, nonsmokers, Asians and patients with adenocarcinoma (p<0.02). QOL measures showed a statistically significant benefit of erlotinib in several patient-reported symptoms including cough, dyspnoea and pain (adjusted p<0.04). Toxicity was similar between the groups, though rash and diarrhoea occurred more frequently in the erlotinib arm.

Authors' conclusions
Neither gefitinib nor erlotinib is beneficial as a first-line treatment for advanced NSCLC in conjunction with first-line platinum-based chemotherapy, nor is gefitinib beneficial as maintenance therapy for patients with NSCLC. However, for patients for whom further chemotherapy is not an option, there is evidence of improved survival, tumour response, symptom control, QOL, and minimal toxicity associated with erlotinib monotherapy as second-line or later treatment. There was no evidence of an association between gefitinib and improved survival among patients with relapsed or recurrent NSCLC, though there was some suggestion that gefitinib may provide symptomatic relief in this population.

CRD commentary
The review question and inclusion criteria were clear. Several relevant sources and strategies were used in a thorough search for primary studies, though the language restriction may have meant that some studies were missed. It is not clear whether adequate steps were taken to minimise the introduction of error and bias during the review process, such as decisions being made independently by more than one author. Moreover, although the authors appropriately took study quality into account in interpreting the results, they did not describe how quality was assessed or systematically report factors such as allocation concealment and blinding in the primary studies. In other respects the characteristics of the included studies were well presented and the narrative synthesis was clear and explicit. The review appears to be generally well-conducted and the conclusions follow the results. However, incomplete reporting of the methods used undermines the strength of the authors' conclusions.

Implications of the review for practice and research
Practice: The authors stated that gefitinib and erlotinib should not be used with first-line platinum-based chemotherapy, nor as maintenance therapy after chemotherapy and radiotherapy, among patients with advanced NSCLC. However, erlotinib monotherapy can be recommended for patients with relapsed or recurrent NSCLC for whom further
Chemotherapy is not an option.

Research: The authors did not state any implications for further research.

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**Indexing Status**
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